A Critical Evaluation of Glycated Protein Parameters in Advanced Nephropathy: A Matter of Life or Death

Time to dispense with the hemoglobin A1C in end-stage kidney disease

Chronic kidney disease remains as one of the major complications for individuals with diabetes and contributes to considerable morbidity. Individuals subjected to dialysis therapy, half of whom are diabetic, experience a mortality of ~20% per year. Understanding factors related to mortality remains a priority. Outside of dialysis units, A1C is unquestioned as the "gold standard" for glycemic control. In the recent past, however, there is evidence in large cohorts of diabetic dialysis patients that A1C at both the higher and lower levels was associated with mortality. Given the unique conditions associated with the metabolic dysregulation in dialysis patients, there is a critical need to identify accurate assays to monitor glycemic control to relate to cardiovascular endpoints. In this two-part point-counterpoint narrative, Drs. Freedman and Kalantar-Zadeh take opposing views on the utility of A1C in relation to cardiovascular disease and survival and as to consideration of use of other short-term markers in glycemia. In the narrative below, Dr. Freedman suggests that glycated albumin may be the preferred glycemic marker in dialysis subjects. In the counterpoint narrative following Dr. Freedman's contribution, Dr. Kalantar-Zadeh defends the use of A1C as the unquestioned gold standard for glycemic management in dialysis subjects.

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An ideal assay for long-term glycemic control in diabetes would accurately reflect recent serum glucose concentrations and predict hypoglycemia- and hyperglycemia-related complications. Hemoglobin A1C (A1C) remains a widely used and trusted tool for assessing glycemic control in patients who lack advanced nephropathy or anemia. The accuracy and predictive ability of the A1C in those with end-stage kidney disease (ESKD) has recently been called into question. The relationship of A1C to serum glucose concentrations changes markedly in advanced nephropathy, as a lower A1C level is seen for similar glucose levels compared with patients without nephropathy. This observation likely reflects shortened erythrocyte (red blood cell; RBC) survival resulting in less time for hemoglobin and glucose to chemically interact. Incorrectly low A1C results in the dialysis clinic produce a false sense of security for patients and clinicians, potentially contributing to the dismal survival rates on dialysis. This article reviews the controversies surrounding the clinical application of A1C in patients with advanced kidney disease. Unadjusted A1C values do not predict outcomes in patients on dialysis. Promising results for glycated albumin (GA) and other glycemic control assays in dialysis populations are reviewed.

Aggressively lowering blood glucose based on A1C targets failed to consistently reduce macrovascular complications in patients with diabetes (1–5), although persisting higher A1C likely contributed to the excess mortality risk in intensively treated Action to Control Cardiovascular Risk in Diabetes (ACCORD) participants (6). In contrast, lowering A1C consistently delays microvascular complications (1–5). There is general agreement that A1C values in the aforementioned studies accurately reflected diabetes control. In contrast, A1C poorly reflects diabetes control in patients with ESKD or stage 5 chronic kidney disease (CKD) (7–11). There remains a critical need to identify accurate assays for measuring recent glycemic control in patients with ESKD, in whom mortality rates are 15–20% per year, predominantly from cardiovascular disease (CVD). Until accurate measures are identified, it will be difficult to clearly determine the effects of better blood glucose control on hospitalization and mortality rates in patients on chronic dialysis therapy.

Two large, retrospective, observational studies assessed the impact of A1C on survival and hospitalization rates in prevalent patients on hemodialysis. The authors reached contradictory conclusions. Critical review of these analyses may allow for common themes to emerge.

Kalantar-Zadeh et al. (12) reported survival rates based on A1C in 23,618 prevalent maintenance dialysis patients with at least one A1C measurement. In an unadjusted analysis, improved survival rates were paradoxically seen in those with the highest A1C, likely reflecting better nutritional status. After adjusting for demographic characteristics and confounders, including dialysis vintage and dose, medical comorbidities, anemia, and measures of malnutrition and inflammation, higher A1C values were associated with a higher risk of death in a graded fashion. The increase in risk of death for rising A1C values was particularly evident in nonanemic patients with hemoglobin concentrations above 11.0 g/dL, demonstrating the importance of longer RBC survival on validity of A1C measurements (13). Subgroup analyses revealed that the association between higher A1C and increased risk of death was more prominent among younger patients, those on dialysis longer than 2 years, and those with higher protein intake, hemoglobin, and serum ferritin concentrations. The authors concluded that, all other things being equal, higher A1C values were associated with increased risk of death on dialysis. Complicated statistical adjustments were required to reach this conclusion, including case-mix (reflecting age, sex, race, preexisting comorbidities, smoking, dialysis vintage, health insurance, marital status, standardized mortality ratio, dialysis dose, type of dialysis access, and residual renal function), and a malnutrition-inflammation complex syndrome adjustment reflecting the aforementioned case-mix covariates plus BMI, erythropoietin dose, and 11 laboratory measures reflecting nutrition and inflammation. This complex analysis is unlikely to be performed by clinicians caring for dialysis patients, thus rendering the use of A1C levels to determine the adequacy of blood glucose management problematic.

Another analysis in 24,875 prevalent maintenance hemodialysis patients revealed

A1C had only weak correlations with mean random glucose values (14). Survival in the subsequent 12-month period ranged from 80 to 85% across all strata of A1C. Kaplan-Meier survival curves grouped by level of A1C demonstrated an absence of correlation between A1C and 12-month survival. Only extremely high and extremely low A1C values were associated with hospitalization rates. No significant effect was observed across the broad range of A1C values between 5.01 and 11.0%, where the vast majority of readings fall. Three-year follow-up in traditional or time-adjusted Cox models demonstrated that only extreme values of A1C associate with survival (15). A report in 1,484 incident dialysis patients from the Alberta Kidney Disease Registry also concluded that A1C values did not predict survival (16).

These three studies included nearly 50,000 dialysis patients and demonstrated that unadjusted A1C values fail to predict survival or hospitalization, although Kalantar-Zadeh et al. (12) detected an effect on survival after intensive statistical adjustment (14,15). There are several potential explanations, not necessarily mutually exclusive, which may account for the lack of an association between A1C and dialysis outcomes. First, glycemic control may not markedly impact CVD outcomes as in nondialysis trials (1–3), just as statins have less of an effect on CVD in dialysis patients (17). Second, unique pathways contribute to CVD in dialysis, including hyperphosphatemia, vitamin D deficiency, and hyperparathyroidism. Finally, the accuracy of the A1C assay is impacted by uremia.

Duong et al. (18) next demonstrated a trend toward association between higher A1C and CVD mortality in 2,798 patients with diabetes on peritoneal dialysis; however, significant association of A1C with survival was limited to nonanemic patients with hemoglobin above 11 g/dL, again reflecting longer RBC survival. As in the prior report by Kalantar-Zadeh et al. (12), complex adjustments were required to reach this conclusion. Importantly, 92% of American dialysis patients perform hemodialysis and the majority have anemia (19). A1C values in peritoneal dialysis patients are most useful in those lacking anemia. Clearly, unadjusted A1C results are not an ideal assay in either hemodialysis or peritoneal dialysis patients.

Relative to ambient glucose concentrations, A1C values are markedly lower in dialysis patients than those without nephropathy. Inaba et al. (8) demonstrated falsely low A1C values in Japanese hemodialysis patients by comparing results to a simultaneous GA; this was followed by reports in African Americans and European Americans (9–11). The U.S. report revealed that patients on hemodialysis had significantly higher mean casual serum glucose and GA concentrations, despite lower A1C compared with nonnephropathy control subjects (11). The GA:A1C ratio was significantly increased in patients on hemodialysis, relative to control subjects lacking nephropathy. A1C was positively associated with hemoglobin concentrations and negatively associated with erythropoietin dosage, whereas these factors and serum albumin concentration did not significantly impact GA. In best-fit multivariate models, hemodialysis status significantly impacted A1C, without significant effect on GA. These studies reveal that A1C levels significantly underestimate glycemic control in patients on hemodialysis, while GA more accurately reflects recent control. Consistent relationships were observed between GA and A1C across populations; the GA:A1C ratio in diabetic patients on hemodialysis, relative to nonnephropathy control subjects was virtually identical in Japanese (3.81/2.93 = 1.30) and Americans (2.72/2.07 = 1.31), demonstrating the bias introduced by A1C. It will be difficult to appropriately adjust A1C values in dialysis patients because of wide variability in hemoglobin, nutritional, and inflammatory parameters. Despite substantially lower erythropoietin requirements, A1C values are also low in patients on peritoneal dialysis and CKD stage 5 predialysis (9,10). These studies were limited by not comparing A1C and GA with fasting blood glucose (20), a factor related to the timing of dialysis shifts; however, this does not alter the main conclusions.

Although GA more accurately reflects recent glycemic control in patients with advanced kidney failure or on dialysis, it remained necessary to prospectively assess the impact of GA on patient survival and hospitalizations. To address this, quarterly GA levels were longitudinally measured in 444 prevalent dialysis patients from an academic dialysis provider; hemodialysis and peritoneal dialysis patients were included (21). Proportional hazard time-dependent covariate models were computed with adjustment for demographic characteristics, comorbidities, and laboratory variables. Similar analyses were performed for A1C and casual serum glucose determinations. Participants were 53% male, 54% African American, and 43% European American. During median follow-up of 2.25 years, 156 deaths were recorded. In best-fit models, significant predictors of death were increasing GA, increasing age, peripheral vascular disease, low serum albumin, and low hemoglobin concentration. For each 5% increase in GA, the risk of death increased by 14%. A1C and casual serum glucose did not predict survival. In addition, higher GA (and higher serum glucose concentration) was associated with hospitalization in the 17 and 30 days after measurement, whereas A1C was not. Restricting the analysis to the 401 patients on hemodialysis, GA significantly predicted risk of death after adjustment for only age, sex, race, and BMI (a trend was present without adjustment), whereas A1C did not. These results complement those of Fukuoka et al. (22), who found that high GA values at dialysis initiation, not A1C, were associated with poorer patient survival after 4 years.

GA reflects glycemic control predominantly during the preceding 17 days, relative to ~30 days for A1C. Both assays have limitations. The GA reference range (mean ± 2 SD) in Americans with normal glucose tolerance is 11.9–15.8%. As for A1C, African Americans have slightly higher values than European Americans (23). The GA assay used in these studies is not yet approved for use in the U.S. by the U.S. Food and Drug Administration; it is available in Asia (7–10). GA can be impacted by albuminuria, cirrhosis, thyroid dysfunction, and smoking. Nonetheless, its usefulness in patients on and near dialysis has been demonstrated; GA outperforms A1C in these settings. Albuminuria typically falls with lower glomerular filtration rates in patients on dialysis, potentially minimizing the effect of albuminuria in ESKD. The superior ability of GA to predict dialysis outcomes cannot be attributed to the serum albumin concentration, analyses adjusted for serum albumin. GA reflects the percentage of albumin that is glycated regardless of total concentration. In contrast, A1C is limited not only by advanced nephropathy but is also subject to error from rapidly changing diabetes control, severe anemia, hemolytic anemia, iron deficiency, recent blood transfusion, HIV positivity treated with antiretroviral therapy, erythropoietin and other drugs interacting with erythropoiesis, and chronic alcohol abuse (24). Although one study suggested that anemia impacted the ability of A1C to predict outcomes in ESKD (18), hemoglobin levels in patients on dialysis

change frequently. Erythropoietin use and hemoglobin concentrations in the U.S. are declining as the result of bundled dialysis payments and a black box warning. As such, higher percentages of dialysis patients will likely manifest low hemoglobin concentrations and require blood transfusions in the near future—factors negatively impacting the prognostic value of A1C.

Although this article focused on GA, other assays and measures of glycated proteins have been evaluated in ESKD. Continuous glucose monitoring (CGM) may prove useful in patients on dialysis. CGM has been evaluated in small numbers of hemodialysis patients (25,26). A strong correlation was observed between CGM and glucose meter readings in hemodialysis patients, whereas fructosamine and A1C readings were poorly correlated with CGM and thus were felt to be less valuable. Kazempour-Ardebili et al. (26) demonstrated lower 24-h mean glucose values and 24-h CGM area under the glucose curve in hemodialysis patients on the day of their treatment, relative to nondialysis days, with frequent episodes of asymptomatic hypoglycemia. In addition, serum albumin–corrected fructosamine may be more tightly correlated with mean serum glucose values below 150 mg/dL in hemodialysis patients relative to A1C; fructosamine also better predicted hospitalizations and infectious complications (27). Finally, care must be exercised when using glucose dehydrogenase pyrroloquinoline quinone glucometers in peritoneal dialysis patients who use icodextrin dialysate, because of interference with the assay and overestimation of serum glucose levels (28).

Is it appropriate to measure A1C in patients with diabetes on dialysis? A1C values are significantly reduced by uremia and shortened RBC survival. They do not reliably predict outcomes in ESKD. CGM remains to be evaluated for effects on survival and hospitalizations in the dialysis population, whereas GA has demonstrated prognostic utility. Prospective studies testing prespecified diabetes control targets based on GA, fructosamine and CGM remain to be performed in order to determine whether survival and hospitalizations would be reduced with intensive glycemic control. In contrast to A1C, GA and CGM appear to have far more promise in this regard. In an era of limited resources, there is no reason to continue measuring A1C in patients with diabetes and ESKD. Despite the shorter half-life of glycemic control, quarterly GA measurements appear adequate and provide useful information to guide physicians in the care of patients with ESKD. Until the GA assay is available, frequent measurements of serum glucose appear more valuable than A1C in patients on dialysis.

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DOI: 10.2337/dc12-0027

Acknowledgments—B.I.F. received research funding from Asahi Kasei Pharma Corporation (Tokyo, Japan). No other potential conflicts of interest relevant to this article were reported.

The support of the Wake Forest Baptist Health Outpatient Dialysis Program staff; Health Systems Management, Inc. (Tifton, GA); Meridian Laboratory Corporation (Charlotte, NC); and Drs. Michael V. Rocco and Anthony J. Bleyer made this research possible.

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